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TITLE: Massage Therapy for Reducing Stress Hormones and Enhancing Immune Function in Breast Cancer Survivors

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13. ABSTRACT (Maximum 200 Words)

In this study massage and relaxation therapies were examined for women with early stages of breast cancer for 1) reducing anxiety and stress hormone levels, 2) decreasing depressed mood and increasing biochemicals associated with decreased depression (serotonin, dopamine), and 3) increasing immune function. 58 women with Stage I-II breast cancer screened for eligibility completed the study: massage (n=22), relaxation (n=20) and control groups (n=16). Women in the massage and relaxation therapies received 3-30 minute sessions a week for 5 weeks. On the first and last days of the 5-week study and at a follow-up period, anxiety and depression levels were assessed, and urine and blood samples were assayed for treatment effects on stress hormones and immune measures. Women in the massage therapy group reported 1) less depressed mood and reduced anxiety, and showed 2) increased dopamine levels, and 3) increased Natural Killer cell numbers; For the relaxation group, findings included 1) a short-term mood improvement and reduction in anxiety. Correlation analyses revealed 1) a positive relationship between anxiety and depression, 2) a negative relation between depressed mood and lymphocytes and 3) that greater dopamine levels related to greater NK cell numbers. The correlation analyses lend support to the hypothesis that mood impacts the neuroendocrine and immunoloigcal profiles of women with breast cancer.
The follow-up assessment 6-months+ later revealed no significant long-term effects suggesting that like many other interventions (e.g., exercise, diet, etc), for therapy effects to persist, continued massage treatments may be required. Taken together, these findings support a step effect with massage therapy having the greatest positive impact on the psychological, biochemical and immunological profiles of women with breast cancer, followed by progressive muscle relaxation therapies, which revealed improved mood short-term.

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Introduction

Breast cancer ranks as the second leading cause of cancer deaths in women (American Cancer Society, 2001). Research reveals that breast cancer patients have elevated stress hormone levels (Van der Pompe, Antoni & Heijnen, 1996), reduced Natural Killer (NK) cell number (Brittenden, Heys, Ross & Eremin, 1996), and impaired NK cell cytotoxicity after surgery (Van der Pompe, Antoni, Visser & Heijnen, 1998). NK cells and NK cell activity play an important role in lysing tumor cells, as well as monitoring and striking against neoplastic (new and abnormal) growth. That chronic stress has been associated with lower NK cell activity (Cohen, Klein, Kuten, et al., 2002), and that women with breast cancer are at risk for elevated stress and reduced NK cell number and NK cell cytotoxicity levels emphasizes the need to find interventions that reduce stress levels for women with breast cancer. The current study was designed to evaluate massage and relaxation therapy effects for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) reducing stress, or anxiety, and biochemical stress levels, 2) decreasing depressed mood and biochemistry associated with depression) and, 3) increasing immune function (i.e., NK cell number, NK cytotoxicity and lymphocytes). During the course of the three-year study (and one-year extension), 60 women diagnosed with Stage I-II breast cancer were to be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). On the first and last day of the 5-week study, measures were to be collected on anxiety and depression (mood), and urine and blood samples were to be assayed for treatment effects on biochemical stress levels and immune measures. A follow-up assessment examined if the effects were long-lived.

Body

Task 1

Over the course of the study period we have screened and trained numerous massage therapists on the protocol developed for the breast cancer massage. We have also developed excellent relations with the breast health center on our medical campus and local support groups, where participants for the study were recruited.

Task 2

Of the participants screened, we have recruited 65 women with early stages of Breast Cancer who met criteria for the study.

Task 3

Of the 65 women recruited, 58 women completed the 5-week protocol for massage (n=22), Relaxation (n=20) and control (n=16). Seven additional women recruited failed to return for their last day's assessments. We had recruited the additional participants to account for attrition. The protocol also included a follow-up visit which we attempted to complete with the one-year extension.

Task 4

Data for the baseline, last day and follow-up of the study for all of the completed participants have been scored and entered into a spreadsheet. We have analyzed these data and have also entered and analyzed the biochemical assays (urine) for the massage, relaxation and control groups, and the immune measure assays (blood) for all three groups. The results from these data analyses are summarized below and presented in Figures at the end of the report. The lab conducting the urine analyses completed all the pending assays and these have been entered.

Participants

Fifty-eight women (M age = 53 yrs old, sd = 11.6) diagnosed with Stage I or II breast cancer (67% mastectomy) recruited from a university cancer center or local support group participated in this study. The 58 women in the study were ethnically distributed: 58% Caucasian, 31% Hispanic and 11% Black, and lower- middle to middle-socioeconomic status (M = 2.7 on the Hollingshead two-factor index). Participants were matched on support group and age and then assigned to a massage therapy group (N=22), relaxation group (N=20) or standard treatment control group (N=16). The massage sessions were 30-minutes long, three times a week for 5-weeks. The relaxation therapy sessions were also 30-minutes long, and 3 times a week and consisted of progressive muscle relaxation (PMR).

Results

On the first and last day of the study, the women completed two self-report questionnaires to measure their mood (POMS) and anxiety levels (STAI). In addition, they provided urine samples, to assay for biochemical stress (cortisol and catecholamines) and mood (serotonin 5HIAA) levels, and their blood was drawn to assay the immune measures (NK cell number, NK cytotoxicity and lymphocytes). A follow-up phase was conducted to assess longer-term effects of the intervention.

Data Analyses

The self-report data subjected to a multivariate analyses of variance (MANOVA) with treatment (massage, relaxation, control) as the grouping variable attained significance, F (12,38) = 2.19, $p < .05$. An inspection of the biochemical and immune measures data revealed that these were not normally distributed. Therefore, non-parametric statistics (Wilcoxon Signed Ranks Tests) were conducted for these and are reported below. Change scores were computed to examine short-term (pre and post) and longer term effects (first and last day) of the intervention across the treatment groups using ANOVAs and Bonferroni alpha corrected t-tests or non-parametric tests when appropriate.

An ANOVA on the POMS depression First Day's change score (pre-to-post) revealed a significant group effect, F (2,56) = 5.51, $p < .05$. Bonferroni t-tests supported the predicted step effect pattern with 1) the massage group reporting the least depressed mood and 2) the relaxation group revealing less depressed mood than the control group. The ANOVA on the STAI anxiety measure revealed a significant group effect on the first day's change scores, F (2,56) = 8.15, $p < .001$ and a marginal group effect on the last session, F (2,56) = 2.44, $p = .09$. Bonferroni t-tests revealed reduced anxiety levels on the first day for the massage and relaxation groups when compared to the control group, and a significant reduction in anxiety only for the massage versus the control group on the last day. The ANOVA on the STAI pre 1st day to pre last day change score to examine longer-term anxiety effects revealed a significant group effect, F (2, 56) = 3.51, $p < .05$, and Bonferroni t-tests revealed a

greater reduction in anxiety only for the massage versus the control group comparison. Figures depicting the above psychological effects are presented at the end of this report.

For the biochemical measures, the massage therapy group revealed only increased dopamine levels, $Z=1.85$, $p < .05$, which corroborates the massage group's self-report of improved mood. The immune measures analyses revealed for 1) the massage therapy group a 12% increase in NK cell number. The relaxation and control group showed no change in immune response (see Figures on Biochemical and Immune Measures).

Finally, the follow-up data revealed no significant changes for any group. This is perhaps not surprising in that the follow-up occurred 6 or more months following the end of the intervention. Like most pharmacological and non-pharmacological interventions (e.g., exercise, diet), for effects to persist the treatment typically needs to continue.

Discussion

The immediate psychological effects for the breast cancer participants who received 5-weeks of massage or relaxation treatment included decreased anxiety and improved mood after the first session. However, only the massage therapy group reported feeling less anxious and in a better mood on the last day of the study, and revealed longer-term reduction in anxiety from the first to the last day of the study suggesting that massage therapy is effective in reducing anxiety and improving mood in women with breast cancer. The increased urinary dopamine levels from the first to the last day of the study corroborated the massaged group's report of improved mood in that an increase in dopamine levels is associated with less depressed mood (Weiss, Demetrikopoulos, West & Bonsall, 2000). The preliminary analyses from last year had also shown an increase in the neurotransmitter serotonin (5-HIAA) for the massage group. However, this did not remain significant after the cells were completed for all groups and the analyses were re-run. The relaxation therapy group also reported improved mood and reduced anxiety, however these effects were short-term and no changes in biochemical levels were observed for the relaxation group. Nonetheless, these findings are still encouraging in that they suggest that progressive muscle relaxation promotes greater relaxation.

Progressive muscle relaxation is a cost-effective therapy that can be practiced anywhere for an immediate reduction in anxiety.

Correlation analyses were also conducted to determine the relations among the self-report, neuroendocrine and immune measures. Results included that the more anxious women (as evident by higher STAI scores) also reported being more angry (on the POMS), $r = .41$, $p < .01$, more depressed, $r = .74$, $p < .001$ and had less vigor (on the POMS), $r = -.44$, $p < .001$. Perhaps this is not surprising given the high comborbidity of these symptoms. Anxiety and anger may be seen as components of depression and emotions associated with a cancer diagnosis. Little research has been conducted on the impact of anger and depression on the immune system of women with breast cancer. Depressed mood also correlated negatively with lymphocyte count, $r = -.27$, $p < .05$, providing support for the hypothesis that mood negatively impacts immune response. Higher dopamine on the first day of the study related to higher NK cell numbers, $r = .40$, $p < .05$, and higher NK cells on the first day of the study related to higher NK cells on the last day of the study, $r = .71$, $p < .001$. Future studies might examine the impact of elevated mood scores on immune measures and stress hormone levels of women with breast cancer.

The critical question for this study was whether massage and/or relaxation therapies would positively impact the immune system of women with breast cancer, as has been shown for HIV. In the current study, the analyses of the immune measures from the first to the last day of the study revealed increased NK cell number only for the massage therapy group. These immune measure changes support the HIV men's massage therapy finding (Ironson, Field, et al., 1996), and a recent HIV adolescent girls' massage therapy study (Diego, et al., 2001), and support the hypothesis of the current study that massage therapy positively impacts the immune system of women with breast cancer. An increase in NK cell activity previously reported for the relaxation group last year was not supported with the larger sample size. However, the self-reported reduced anxiety and improved mood after the first treatment are encouraging as these suggest that progressive muscle relaxation therapy (like massage therapy) may be effective for attenuating psychological symptoms known to have

adverse effects on breast cancer patients. In sum, the results from this research support our original hypothesis that massage therapy improves the psychological, biochemical and immunological responses of women diagnosed with early stages of breast cancer and that relaxation therapy promotes greater relaxation for these patients.

Key Research Accomplishments

- Screened and recruited 65 women with breast cancer.
- Completed treatment protocol for 58 women
- Scored, entered and analyzed the self-report data for all completed subjects.
- Entered and analyzed the biochemical and immune measures' data.
- Comparison of 1st versus last day's measures for women in the massage therapy group support our hypotheses that massage:
    - **a)** decreases stress (or anxiety) and improves mood
    - **b)** affects the biochemistry of the breast cancer participants in a positive manner, as evident by an increase in urinary dopamine levels for the massage group
    - **c)** positively affects the immune system as evident by an increase in Natural Killer cell number.
- The progressive muscle relaxation therapy measures revealed:
    - a) decreased anxiety and improved mood following the first session.
- That the 6-months follow-up assessments failed to reveal significant effects is perhaps not surprising as it suggests that massage treatments may need to continue (like exercise) in order for the effects to continue.
- Correlation analyses revealed interrelations among the psychological, neuroendocrine and immunological functions of women with breast cancer in that
    - a) greater anxiety correlated with greater anger, depression and less vigor.
    - b) greater depression correlated with lowered lymphocyte count and
    - c) higher dopamine related to higher NK cell number.

Reportable Outcomes

Conference Presentations

Ironson, G., (2002). "Impact of Massage on Biology and Well-Being in Cancer and Aids Patients." Paper presented August 14, 2002 at the Second Annual DOD Population Health and Health Promotion Conference, Baltimore, MD.

Ironson, G. (2002). "Massage Therapy for Reducing Stress Hormones and Enhancing Immune Function in Breast Cancer Survivors (BC980215). Paper presented September 2002 at the DOD Era of Hope Conference.

Manuscripts:

Hernandez-Reif, M., Ironson, G., Field, T., Hurley, J., Katz, G., Diego, M., Weiss, S., Fletcher, M., Schanberg, S., & Kuhn, C. (2003). Breast Cancer patients have improved immune and neuroendocrine functions following massage therapy. (in press with the Journal of Psychosomatic Research).

Hernandez-Reif, M., Field, T., Ironson, G., Hurley, J., G., Beutler, J., Vera, Y., Fletcher, M., Schanberg, S., & Kuhn, C. (2001). Breast Cancer patients report reduced depression, anxiety and pain with progressive muscle relaxation therapy and with massage therapy and show increased neuroendocrine and immune response following massage therapy (manuscript in preparation).

*** Please note that the second manuscript included additional measures which were supported by gift funds from a massage oil company.

Funding applied for based on work supported by this award: (none funded)

1. Ovarian Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.
2. Prostate Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.
3. Breast Cancer, Massage vs Sham Massage, IDEA Award, DOD.

Conclusions

The study's findings imply that breast cancer patients may benefit from massage and relaxation therapies. Specifically, the findings revealed that massage therapy was associated with 1) reduced anxiety and depressed mood, 2) increased urinary dopamine values and 3) increased NK cell numbers from the first to the last day of the study. These findings support the hypothesis that massage therapy has a positive impact on the psychological, biochemical and immunological functions of women with breast cancer. The findings were also positive for women with breast cancer who received progressive muscle relaxation therapy and included reduced anxiety and depressed mood after the

first session. Because progressive muscle relaxation can be conducted at home by listening to an audiotape, this suggests that it can be a cost-effective intervention for women with breast cancer.

"So What"

The findings from this research project showed that women with early stages of breast cancer benefited from massage and relaxation therapies. Findings associated with these therapies included reduced anxiety and improved mood, and additionally for the massage group biochemical and immunological benefits. Because these therapies proved to be therapeutic and are non-invasive, pose no side effects or interactions with medications, they should be considered as adjunct therapies for women with breast cancer. Although most women will probably prefer massage therapy, it is not covered by most insurance carriers. Perhaps a significant other, friend or family member of the breast cancer patient could be trained to conduct the massage protocol, as we have in other studies (e.g., depressed pregnant women), to make massage therapy more cost-effective. One advantage to relaxation therapy is that it is already cost-effective in that women can conduct relaxation sessions at home or anywhere by listening to an audiotape. The findings also support that massage and relaxation therapies were well received by an ethnically diverse group of women with breast cancer, suggesting the generalizability of the therapies across at least three different races. In summary, massage and relaxation therapies when offered in conjunction with standard care, may improve the quality of life of women undergoing the stressors of living with a life-threatening disease. Moreover, in that massage therapy positively impacted so many different aspects of functioning (psychological, biochemical and immunological), warrants further study of massage therapies for breast cancer survivors.

References

American Cancer Society, Inc (2001). Breast Cancer Facts and Figures 2001-2002. 01-50M-No. 8610.01-R, Atlanta, Ga.

Brittenden J, Heys S, Ross J, Eremin O. (1996). Natural killer cells and cancer. Cancer, 77, 1226-43.

Cohen, M., Klein, E., Kuten, A., Fried, G.,Zinder, O., & Pollack, S. (2002). Increased emotional distress in daughters of breast cancer patients is associated with decreased natural cytotoxic activity, elevated levels of stress hormones and decreased secretion of Th1 cytokines. International Journal of Cancer, 100, 347-354.

Diego, M., Field, T., & Hernandez-Reif, M., Friedman, L., & Shaw, K. (2001). HIV adolescents show improved immune function following massage therapy. International Journal of Neuroscience, 106, 35-45.

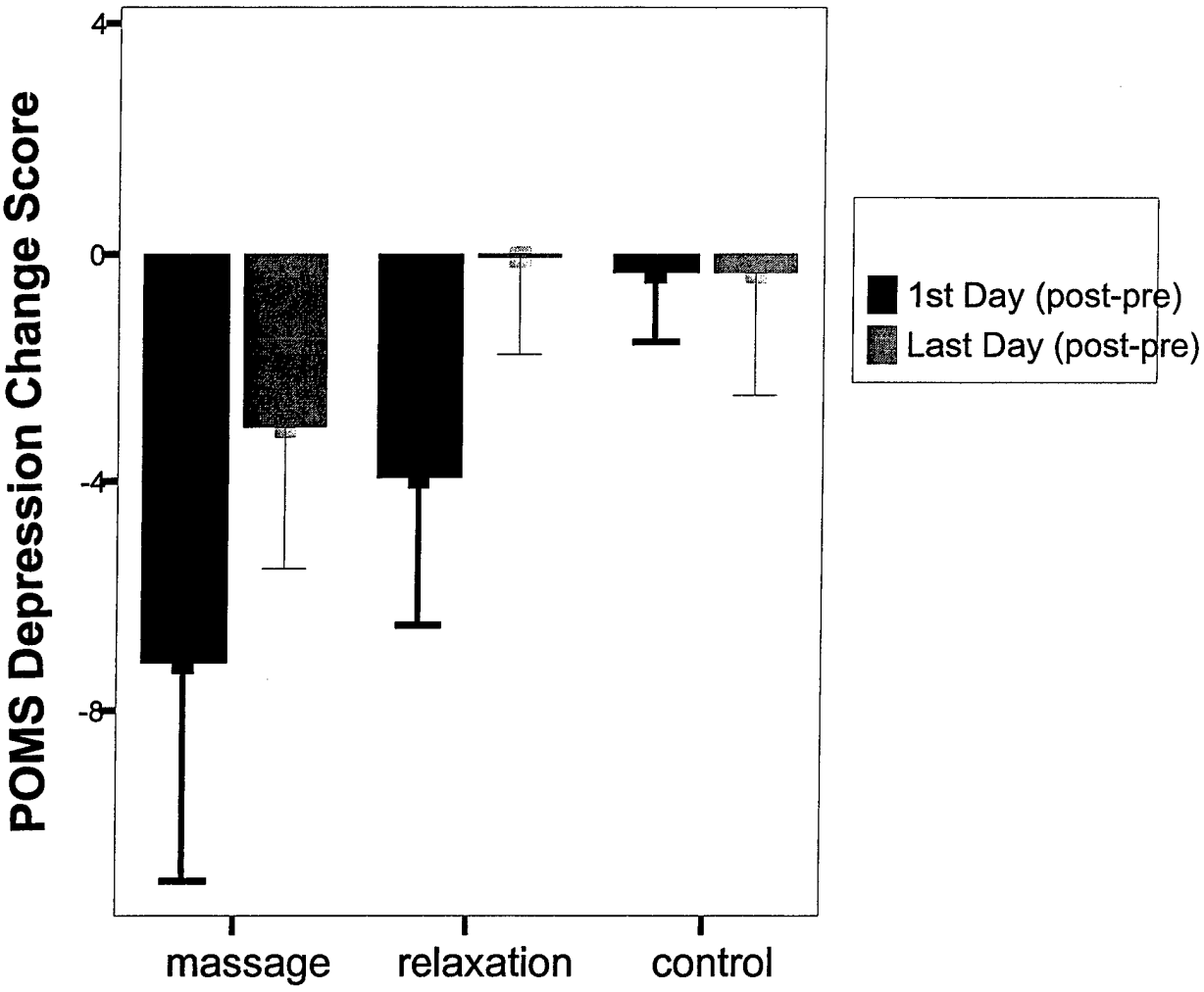
Ironson G, Field T, Scafidi F, Kumar M, et al. (1996). Massage therapy is associated with enhancement of the immune system's cytoxic capacity. International Journal of Neuroscience, 84,205-17.

Van der Pompe, G., Antoni, M., & Heijnen, C. (1996). Elevated basal cortisol levels and attenuated ACTH and cortisol responses to a behavioral challenge in women with metastatic breast cancer. Psychoneuroendocrinology, 21, 361-374.

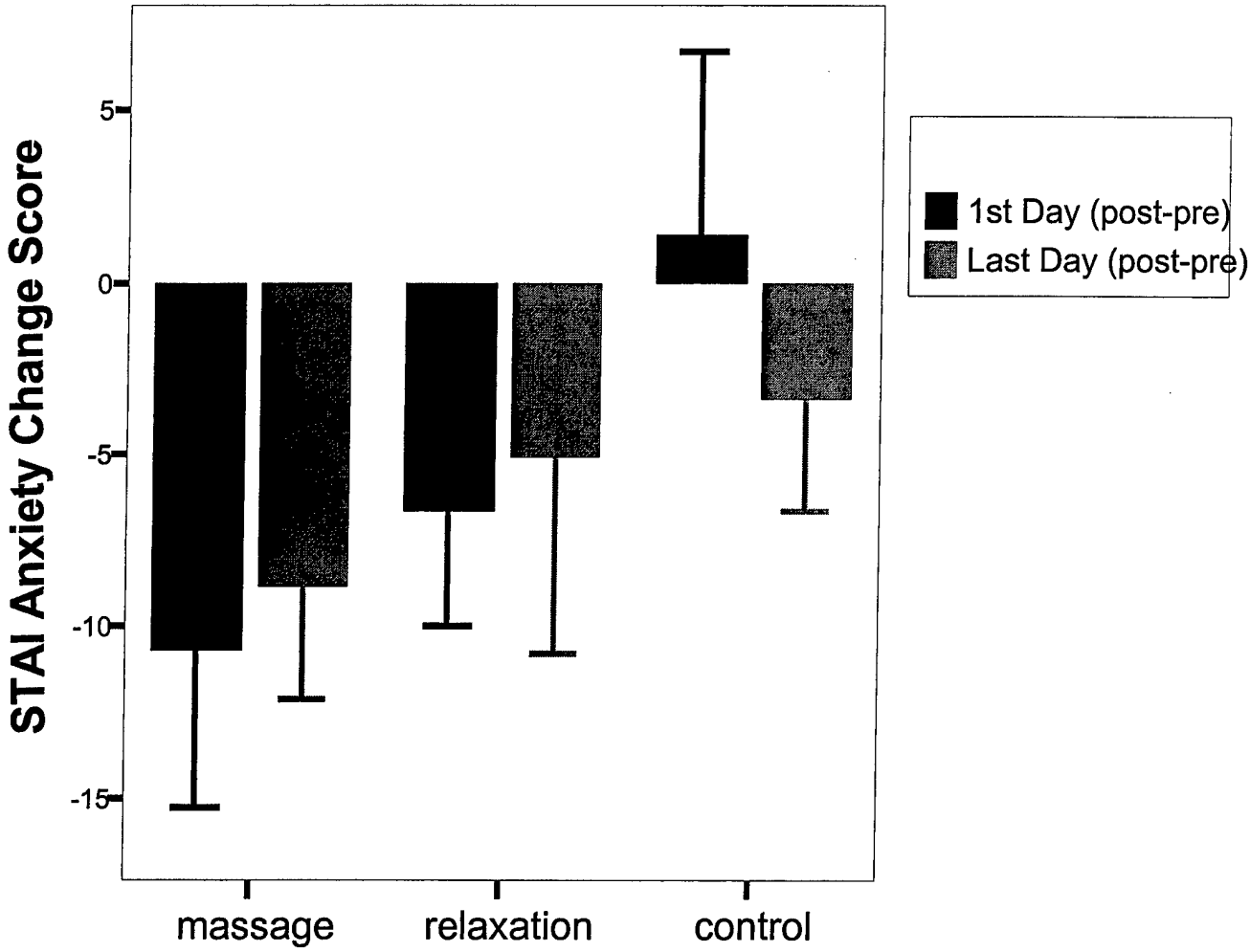
Van der Pompe G, Antoni M, Visser A, Heijnen C. (1998). Effect of mild acute stress on immune cell distribution and natural killer cell activity in breast cancer patients. Biological Psychology, 48, 21-35.

Weiss J, Demetrikopoulos M, West C, Bonsall R. (2000) An hypothesis linking the noradrenergic and domapinergic symptoms in depression (in press).

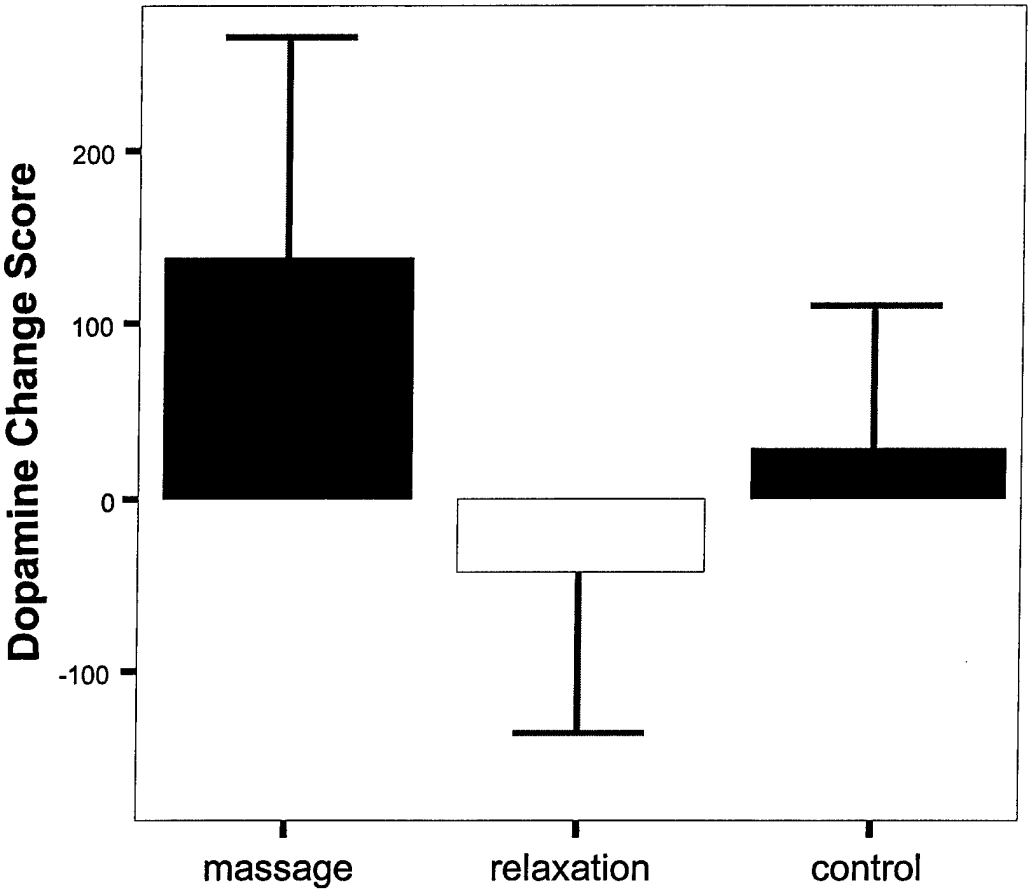
Change Score Means and Error Bars for POMS Depressed Mood (Immediate Effects) on the First and Last day of Study



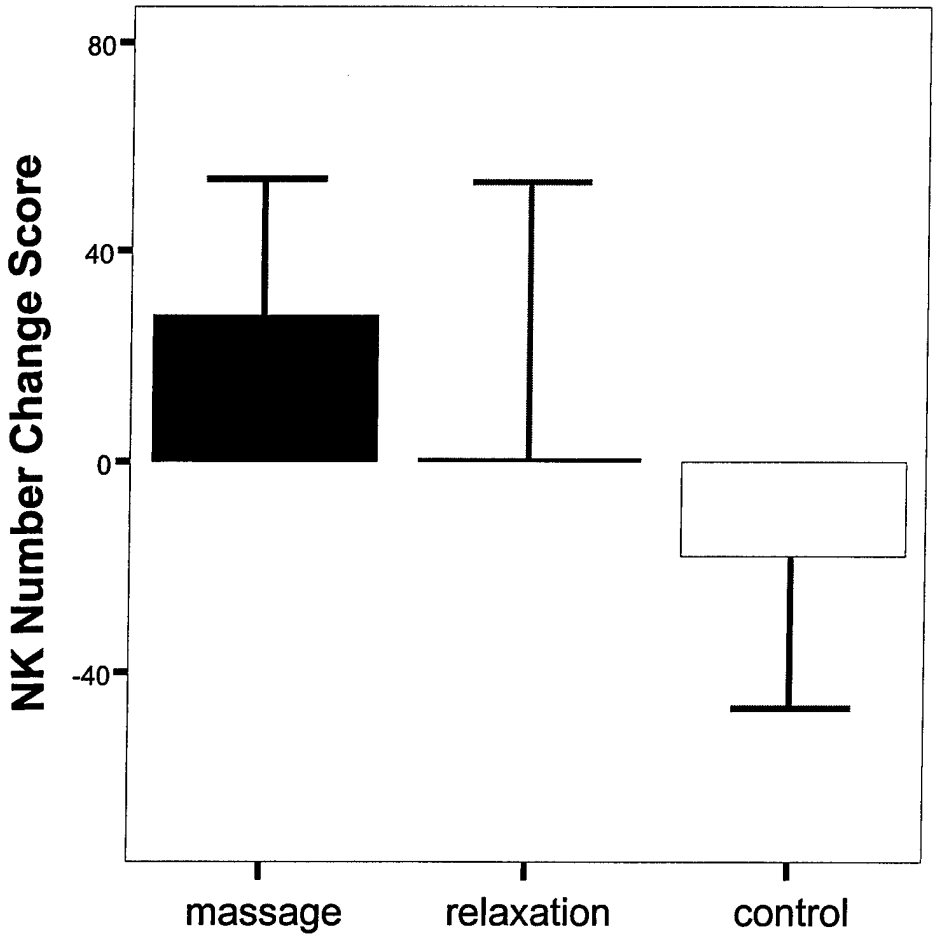
Change Score Means and Error Bars for STAI Anxiety (Immediate Effects) on the First and Last day of Study.



Dopamine Change from First to Last Day for Massage Therapy, Relaxation Therapy and Control Group.



NK Cell Number Change from First to Last Day for Massage Therapy, Relaxation Therapy and Control Group.



Bibliography

See Reportable Outcomes for papers in review and abstract presentations

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